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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/025,732	12/19/2001	William M. Pardridge	0180.0029	8416

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EXAMINER	
LAMBERTSON, DAVID A	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/025,732	PARDRIDGE, WILLIAM M.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 23-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 23-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a reply to the previous Office Action, filed July 19, 2004. Amendments were made to the claims.

Claims 1-10 and 23-29 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, mailed March 22, 2004, that is not addressed in this action has been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 and 23-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is necessitated by amendment of the claims to again recite the use of therapeutic genes; as such, subject matter from the initial rejection (mailed September 23, 2003) has been reiterated to make the current record clear with regard to the instant claims.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is

a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), and the most relevant factors are indicated below:

Nature of the invention. The nature of the invention is a receptor-specific liposome for the delivery of a therapeutic or diagnostic agent across the blood-retinal barrier (BRB) or ocular cell membrane (OCM) followed by the expression of the therapeutic or diagnostic agent in the recipient cells. Two asserted utilities are set forth in the instant specification: a gene therapy use which is prevalent throughout the specification, and a diagnostic use; support for the diagnostic use is indicated by Applicant (as per previous remarks in responses to previous Office Actions) to be present at paragraph [0039] where it is stated "the therapeutic gene which is encapsulated within the liposome can be any of the common therapeutic genes which are used to express therapeutic and diagnostic agents." However, there is no indication of what is diagnosed by the delivery and expression of these genes across the BRB or OCM; for example, if arrestin (a particular gene recited as having therapeutic and/or diagnostic value) is delivered across the BRB, there is no indication of what is diagnosed, other than that the gene had been delivered across the BRB.

Breadth of the claims. The claims are very broad, encompassing the delivery of a vast number of genes across the BRB or OCM; this requires that the vast number of delivered genes be applicable to some therapeutic or diagnostic purpose. In other words, one must be able to treat a condition or diagnose a condition by delivering and expressing a given gene across the BRB or OCM.

State of the art. As it regard the potential therapeutic (i.e., gene therapy) use of the claimed invention (i.e., when a therapeutic gene is delivered by the liposome), the state of the art indicates the unpredictable and controversial nature of gene therapy. Verma (as cited in previous Office Actions) indicates that many pitfalls persist regarding gene therapy techniques, including determining how much of a gene should be delivered to attain a therapeutic value, how to successfully target and deliver a therapeutic agent to the desired location *in vivo*, and how to sustain the expression of the therapeutic gene to achieve a therapeutic result (again see page 293, right and center columns of Verma). Verma further states specifically that the use of cationic lipids (i.e., liposomes) for gene therapy purposes suffers from an inability to efficiently deliver and sustain the expression of therapeutic genes. The unpredictable nature of gene therapy was further evidenced in 2003 when patients who were treated for SCID via gene therapy began to unexpectedly develop a particular form of cancer, believed to result from the improper insertion of the delivered gene into a specific gene in the target cells (see Check, as recited in the previous Office Action).

As it regards the use of a given gene for diagnostic purposes, there is no teaching in the state of the art that would direct the skilled artisan as to how the exogenous expression of a given gene (e.g., arrestin) would be diagnostic of anything. Indeed, it seems the only diagnosis that can be gleaned from such an endeavor concerns the ability of the liposome to deliver the particular gene into a cell.

In conclusion, the skilled artisan would not be able to consult the prior art to use the invention for either a therapeutic or diagnostic purpose, due to the unpredictability of gene therapy as established by the Verma and the Check references, and the lack of a clear diagnostic

purpose for delivering an exogenous gene across the BRB or OCM. As such, the skilled artisan would be required to consult the instant specification in order to practice the claimed invention.

Number of working examples and Guidance provided by applicant. The instant specification does not provide sufficient guidance to overcome the deficiencies in the state of the art as it regards gene therapy. There is no indication as to which genes can be used to treat particular conditions, what amounts of any given gene must be expressed to elicit a therapeutic effect, or how to accomplish that level of expression, especially given the state of the art which indicates the difficulties with sustaining expression of a therapeutic gene. Furthermore, there is no guidance as it regards using a given gene for a diagnostic purpose. The only guidance in the specification regarding a diagnostic use is a single paragraph ([0039]), which provides no specific guidance as to which genes diagnose which characteristics, conditions, etc. The only example set forth in the instant specification is the transitory expression of β-galactosidase in ocular cells, *in vitro*. However, this serves no therapeutic or diagnostic purpose, other than to simply show that β-galactosidase can be delivered by a liposome and expressed in ocular cells. There is no condition that is treated or diagnosed simply by delivering and expressing β-galactosidase in an ocular cell. The expression, being transitory, does not meet any therapeutic threshold, nor does the expression *in vitro* demonstrate that such delivery or expression can be accomplished in an *in vivo* environment. Thus, the instant specification does not appear to overcome the deficiencies of the state of the art as it regards either a therapeutic or a diagnostic use for the claimed invention.

Unpredictability of the art and Amount of experimentation required. The claimed invention is highly unpredictable as it regards the ability to use the invention. The instant specification

asserts a therapeutic and a diagnostic utility for the invention. However, the state of the art indicates not only that gene therapy is a highly underdeveloped and unpredictable field; it is also silent on how to use the exogenous expression of a gene for diagnostic purposes. The instant specification does not provide sufficient guidance or examples to overcome the deficiencies of the prior art. As such, the skilled artisan would have to empirically determine what genes can be used to treat a vast number of conditions associated with ocular cells and how to efficiently deliver and sustain the expression of that gene in a cell to achieve a therapeutic effect. This is an undue and unpredictable amount of experimentation, especially in light of the fact that the state of the art indicates how much difficulty has been encountered with regard to gene therapy. As it regards a diagnostic purpose, the skilled artisan would be required to empirically determine diagnostic parameters for a given gene; essentially, the skilled artisan would be required to find a use for the claimed invention as it regards a therapeutic role. As a result of the unpredictable nature of the claimed invention and the undue amount of unpredictable trial and error experimentation required to use the claimed invention, the instant claims lack enablement.

Response to Arguments Concerning Claim Rejections - 35 USC § 112

Applicant's arguments filed July 19, 2004 have been fully considered but they are not persuasive. The following grounds of traversal are set forth:

1. It is argued that the term "therapeutic gene' is not being used to indicate that the gene actually has a therapeutic purpose, but rather to provide guidance as to what types of genes are suitable for delivery using the claimed liposome (see for example page 6, second full paragraph of Applicant's Remarks).

2. It is argued that the instant specification, indeed even claim 3, provides a plethora of suitable genes that could be used as "exemplary therapeutic and diagnostic agents that are used in investigating and treating ocular cells," and thus can be contained within the claimed liposomes (see for example pages=6-7, the bridging paragraph of Applicant's Remarks).

3. It is argued that the claims are not directed to methods of using the claimed invention (i.e., a method of treating or diagnosing a condition), and it is alleged that there is no requirement to enable a non-claimed invention under 35 USC § 112, first paragraph. An example is then provided whereby liposomes of the claimed invention and ocular cells are mixed either *in vivo* or *in vitro*, wherein the end results are irrelevant (see for example page 7, second full paragraph of Applicant's Remarks).

4. It is alleged that there are a "wide variety of existing and potential future uses with respect to delivering genes to ocular cells" (see for example page 7-8, bridging paragraph of Applicant's Remarks).

Applicant's arguments have been fully considered, but are not convincing for the following reasons:

1. The claims are not the proper location in which to provide guidance; that is the purpose of the specification. When an element is placed into a claim, that specific embodiment is being claimed and must satisfy the statues, including 35 USC § 112, first paragraph. In the instant case, protection is sought for a liposome that carries a therapeutic gene; as such, the embodiment must have an enabled use. Despite Applicant's arguments to the contrary, the term "therapeutic gene" carries a connotation that the gene have some treatment capacity (i.e., it must actually be

"therapeutic"), there being no definition in the instant specification providing contrary information. Indeed, the instant specification is replete with references to expressing a given gene in ocular cells fro treatment purposes (see for example paragraphs [0013], [0039] and throughout), thus there is a contemplated and asserted therapeutic utility for the claimed invention. Furthermore, Applicant's own arguments continue to indicate that the liposomes can be used for treatment of conditions (see for example the first line of the third paragraph on page 6 of Applicant's remarks). As such, Applicant's argument that the term "therapeutic gene" carries no therapeutic activity is misplaced. Indeed, the instant specification clearly indicates that a therapeutic purpose is inherent to the claimed invention. As such, this argument is not convincing.

2. The enablement issue in the instant case is not a question of *making* the invention, but rather a question of *using* the invention, which is also required under 35 USC § 112, first paragraph. As previously stated and reiterated above in the instant rejection, the asserted utilities of the claimed invention are therapeutic and diagnostic. Thus, the skilled artisan must be able *to use* the claimed invention in view of the asserted utilities for the claimed invention. However, as adequately established in the rejections, the state of the art indicates the unpredictability of gene therapy, especially when using liposomes as the delivery vector, and the instant specification does not overcome these deficiencies. The same is true with regard to the asserted diagnostic utility. If one were to express arrestin, α-transducin or rhodopsin kinase in an ocular cell using the claimed liposomes, what would this diagnose other than the ability to express an exogenous gene in a cell? Since there is no clear guidance in the specification as to what can be diagnosed simply by exogenously expressing a gene in a cell, and because the instant specification cannot

overcome the deficiencies established by the state of the art of gene therapy, the skilled artisan is unable *to use* the invention without unpredictable and undue trial and error experimentation.

3. While it is true that, when claiming a product, Applicant does not have to enable non-claimed inventions *per se*, the claimed invention still must have an enabled use commensurate with the asserted utility for the claimed product. If there is no enabled use for the product, the product itself cannot be enabled. In the instant case, the specification asserts that the claimed invention can be used for therapeutic (i.e., treatment) and diagnostic purposes; as such, in order to satisfy 35 USC § 112, first paragraph, the skilled artisan must not only be able to make the claimed invention, but must also be able to use the invention for a therapeutic or diagnostic purpose. One cannot claim a product that has no enabled use simply because there are no claims drawn to using the claimed product. As such, Applicant's assertion that the claims need not be enabled in terms of using the claimed product is misplaced, thus the argument is found unconvincing.

4. The fact that there are future potential uses for the claimed invention cannot be used to establish an enabled use for the claimed invention. The invention must be enabled at the time of filing, and not post-filing. If there are future potential uses for the claimed invention, it is impossible for the instant specification to teach one of skill in the art how to use the invention for the future purpose because these future potential uses remain unknown. As it relates to the asserted utilities of the instant invention, it is reiterated that neither the instant specification nor the state of the art teaches the skilled artisan how *to use* the invention. Although, in the future, the unpredictable nature of gene therapy may be resolved and one may develop a diagnostic test involving the exogenous expression of a gene in an ocular cell, the instant specification does not

teach the skilled artisan how to accomplish these tasks. As such, the instantly claimed invention cannot be enabled for future uses.

In conclusion, Applicant's arguments have not been found convincing. Despite arguments to the contrary, the recitation of the term "therapeutic gene" requires a therapeutic use for the claimed invention. This is irrespective of the fact that a method of using the claimed invention is not immediately claimed; a product must still have an enabled use. Requiring a product to have an enabled use, therefore, is not in conflict with 35 USC § 112, first paragraph. Thus, the rejection under 35 USC § 112, first paragraph is maintained as reiterated above in view of the amendments to the claims.

Allowable Subject Matter

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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PRIMARY EXAMINER